

Smoke Inhalation Injury and the Effect of Carbon Monoxide in the Sheep Model

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The role of carbon monoxide (CO) in causing the physiologic and anatomic changes characteristic of smoke inhalation injury was evaluated in 34 sheep. The smoke-exposed group received a dose of smoke known to produce mild inhalation injury. The CO group received a pure gas mixture that contained concentrations of oxygen, carbon dioxide, and CO similar to those in the smoke. Cardiopulmonary function was measured immediately after exposure, and 24 and 72 hours after exposure. The CO group showed a transient increase in cardiac output, but the smoke group showed no such response. The CO group maintained normal PaO₂ levels during the 72-hour study period; the smoke group gradually developed hypoxemia. The lungs of the CO exposed animals had no discernible histologic changes; lungs of the smoke group showed progressive inflammatory changes. These results indicate that CO per se is not the primary etiologic agent of smoke inhalation injury.

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Smoke inhalation injury, one of the primary determinants of survival following major burns (11), is characterized by progressive inflammatory changes resulting in deterioration of pulmonary function and structure (16). Smoke contains numerous toxic substances and, although no single substance appears to be responsible for all the changes that occur after smoke inhalation (19, 23), carbon monoxide (CO) is one of the major combustion products that may reach lethal levels in actual exposures producing inhalation injury (2, 10).

Carbon monoxide poisoning is primarily responsible for fire deaths that occur acutely after smoke inhalation (24). However, the effects of nonlethal carbon monoxide poisoning in the pathogenesis of smoke inhalation injury have not been fully evaluated. Conflicting results have been obtained in clinical and animal studies of the tox-

icity of carbon monoxide (5, 7). Sharar et al. recently pointed out that there is a great discrepancy in the relationship between peak carboxyhemoglobin (CO-Hb) levels and mortality among various animal models of smoke inhalation injury; in one animal model a 20% peak carboxyhemoglobin (CO-Hb) level was the LD₅₀, while in another model a 37% peak CO-Hb level was attended by no deaths in 24 hours (15).

In this study, we have examined the effects of acute carbon monoxide exposure on cardiopulmonary function and on the structure of the lung and compared them with those associated with smoke inhalation injury producing comparable levels of blood CO-Hb.

MATERIALS AND METHODS

Animals. Thirty-four male sheep 1-2 years old weighing 25 to 40 kg were used in this study. Six sheep served as controls and a randomly selected smoke exposed group ($n = 14$) received a dose of smoke which in a previous study had caused mild changes in the respiratory system (16). A carbon monoxide (CO) treatment group ($n = 14$) received a pure gas mixture that contained amounts of oxygen, carbon dioxide, and carbon monoxide similar to those in the smoke. Of the 14 sheep in each of the treatment groups, four were studied 1 hour after exposure, five 24 hours after exposure, and another five 72 hours after exposure.

Smoke and CO Gas Exposure. Smoke was produced by burning ten disposable underpads made of polyethylene, wood pulp, and nonwoven cellulose fabric. The smoke reached ambient temperature during passage through the smoke delivery system and contained 10-14% oxygen, 3-8% carbon dioxide, and 0.7-2.2% carbon monoxide. The pure gas mixture used for the CO exposure group contained 12.6% oxygen, 5.2% carbon dioxide, 2.0% carbon monoxide, and 80.2% nitrogen.

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In conducting the research described in this report, the investigators adhered to the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and with the *Guide for the Care and Use of Laboratory Animals*, National Institutes of Health Publication 85-23.

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The sheep were intubated, anesthetized with methohexital sodium (9 mg/kg, Brevital Sodium, Eli Lilly and Company, Indianapolis, IN), and paralyzed with succinylcholine chloride (0.7 mg/kg). The animals were then insufflated with either smoke or the CO gas mixture for 5 minutes with intermittent room air ventilation as described previously (16). The sheep were extubated after exposure.

Hemodynamic and Pulmonary Measurements. At the times selected for physiologic studies, anesthesia was induced with methohexital sodium (9 mg/kg) and maintained with alpha-chloralose (0.05 g/kg, Calbiochem, La Jolla, CA), and the sheep were paralyzed with pancuronium bromide (0.03–0.04 mg/kg) (16). Arterial and central venous lines, a Swan-Ganz catheter (7F, American Edwards Laboratories, Irvine, CA), and an esophageal balloon were then inserted. After the placement of catheters, the animals were positioned prone and artificially ventilated with an inspired FIO_2 of 0.21, employing a tidal volume of 15 ml/kg at a respiratory rate of 12 per minute (Bear 2 ventilator, Bear Medical Systems, Inc., Riverside, CA) without positive end-expiratory pressure. Lactated Ringer's solution was continuously infused at a rate of 1 ml/kg per hour.

Systemic arterial pressure, central venous pressure, and pulmonary arterial pressure were monitored and recorded continuously. Transpulmonary pressure, flow rate, and tidal volume were measured to calculate airway resistance and static pulmonary compliance. Cardiac output was measured in triplicate by thermodilution technique (cardiac output computer, Model 9520A, American Edwards Laboratories). Blood gas analysis was performed using an IL 1303 pH/blood gas analyzer and an IL 282 CO-Oximeter (Instrumentation Laboratories, Inc., Lexington, MA). These indices and blood gas levels were measured every 30 minutes, and the values measured after 2 hours of stabilization were taken as representative values.

At the conclusion of the physiologic studies all sheep were sacrificed with barbiturate and potassium chloride, and necropsies were performed for histologic examination including electron microscopy.

Data are shown as mean \pm standard deviation. Statistical significance was tested between the smoke and the CO groups by independent *t*-tests; interaction between time of measurement and the gas (smoke or CO) to which the animals were exposed was evaluated by analysis of variance (4). Significance was assigned when the *p*-value of the difference between groups at one time was less than 0.016 (0.05/3), giving an overall *p*-value of 0.05 or less for comparisons at 1, 24, and 72 hours after exposure.

RESULTS

None of the sheep exposed to smoke or CO gas mixture died during the study period. Although some of the smoke-exposed animals showed signs of mild respiratory distress after 48 hours, they could breathe spontaneously and stand unassisted.

Mean venous carboxyhemoglobin (CO-Hb) levels immediately after smoke and CO exposure were $57.0 \pm 8.9\%$ ($n = 14$) and $56.3 \pm 9.1\%$ ($n = 14$), respectively.

The arterial PO_2 levels are shown in Figure 1. The controls had an average PaO_2 of 91.3 ± 3.7 torr. The CO-exposed sheep showed no change in PO_2 at any time, while the smoke-exposed group showed an initial slight decline at 1 hour, recovered by 24 hours, and then developed a statistically significant hypoxemia at 72 hours. $PaCO_2$, on the other hand, was maintained in both groups

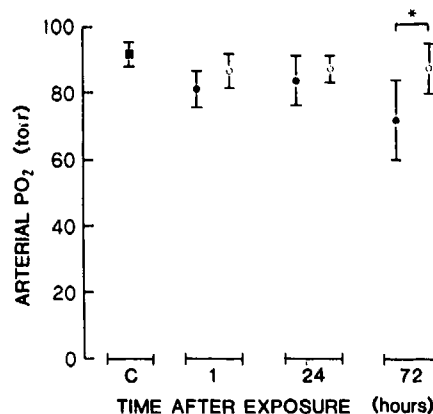


FIG. 1. Arterial oxygen tension (PaO_2) of the smoke (closed circles) and carbon monoxide (open circles) exposed groups at one, 24, and 72 hours after exposure. C stands for controls. Mean \pm standard deviation. (*) indicates $p < 0.05$. The CO group maintained a normal PaO_2 level, while the smoke group had a significantly lower PaO_2 at 72 hours.

and showed no significant difference at any time (Table I).

Figure 2 depicts changes in cardiac index. Cardiac index was maintained in the smoke-exposed group and remained essentially constant across time, while the CO-exposed animals showed an initial significant increase at 1 hour after exposure and then returned to normal at 24 and 72 hours. The cardiac index of the CO-exposed sheep at 1 hour was significantly higher than that in the control and the smoke-exposed groups.

Oxygen tension of the mixed-venous blood ($P\bar{v}O_2$) was significantly lower in the smoke-exposed group at 1 hour (Table I). Oxygen utilization was thus maintained without an increase in cardiac index.

There were no significant differences in mean pulmonary arterial pressure (mPAP), total peripheral resistance index (TPRI), lung water, or oxygen consumption (Table I). Left ventricular stroke work index (LVSWI) was not significantly elevated in the CO group at 1 hour, associated with the markedly increased cardiac index.

Figure 3 depicts changes in pulmonary resistance (PR). PR is calculated from the equation $PR = (\text{mouth pressure} - \text{intrapleural pressure}) / \text{flow rate}$, and includes both airway resistance and pulmonary tissue resistance. PR was significantly higher in the smoke group at 1 hour, but this change was not distinct at or after 24 hours. PR in the CO group did not differ from the control at any time. Changes in static compliance were the reciprocal of those in PR (Fig. 4). The seemingly lower compliance of the smoke group at 1 hour after exposure was not statistically significant.

Histologic examination revealed a sequence of histopathologic changes in the smoke-exposed animals that progressed in a predictable fashion, as reported previously (9, 16). There were no histologic changes in the lungs of CO-exposed animals at any time that were directly attributable to CO exposure.

Figure 5 shows scanning electron micrographs of the tracheal surface 24 hours after exposure. Normal cilia

TABLE I
Selected cardiopulmonary indices (mean \pm SD)

	Control	Smoke			CO		
		1 hr	24 hr	72 hr	1 hr	24 hr	72 hr
PvO ₂ (torr)	38.2 \pm 3.6	20.6 \pm 3.4*	40.5 \pm 1.8	32.3 \pm 3.2	28.0 \pm 2.8	38.5 \pm 6.6	40.6 \pm 2.9
PaCO ₂ (torr)	28.8 \pm 5.0	28.0 \pm 4.8	31.2 \pm 2.8	30.8 \pm 3.6	31.3 \pm 3.7	29.4 \pm 3.8	27.2 \pm 1.7
mPAP (torr)	10.9 \pm 1.9	15.0 \pm 2.6	10.8 \pm 3.4	12.5 \pm 3.8	12.4 \pm 4.2	13.9 \pm 1.7	14.9 \pm 4.0
LVSwt† (g·m/m ²)	30.8 \pm 4.7	31.8 \pm 6.3	41.0 \pm 3.9	28.3 \pm 6.0	61.4 \pm 9.1*	37.9 \pm 8.4	43.6 \pm 7.5
TPRI‡	2,596 \pm 210	2,507 \pm 759	2,649 \pm 521	2,660 \pm 555	1,704 \pm 312	2,822 \pm 563	2,751 \pm 601
Lung water (ml/kg)	10.3 \pm 1.2	9.6 \pm 1.9	10.8 \pm 1.0	12.2 \pm 1.4	12.2 \pm 2.1	11.3 \pm 0.8	10.3 \pm 0.5
VO ₂ (ml/min)	164 \pm 15	201 \pm 24	150 \pm 14	171 \pm 20	171 \pm 29	141 \pm 9	165 \pm 9

* $p < 0.01$ by ANOVA.

† LVSwt = left ventricular stroke work index.

‡ TPRI = total peripheral resistance index (dynes \times sec \times m²/cm⁵).

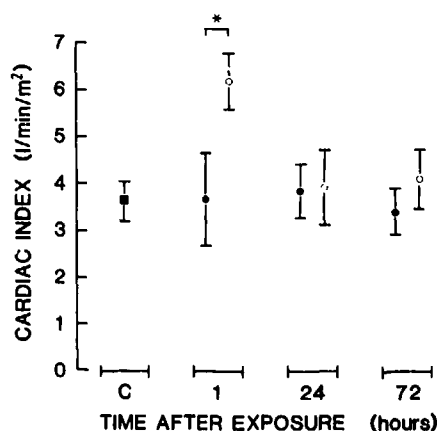


FIG. 2. Changes in cardiac index (CI) after smoke or CO exposure. Refer to Fig. 1 legend for symbols and abbreviations. The CO group had significant elevation of cardiac index immediately after exposure (time = 1 hr).

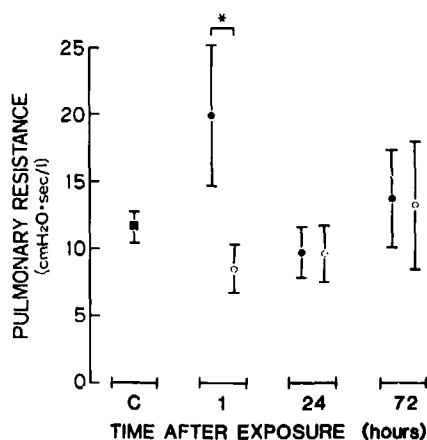


FIG. 3. Changes in pulmonary resistance (PR). The smoke group had significant elevation of PR 1 hour after exposure.

are preserved in the CO-exposed animal (Fig. 5A), whereas marked disruption and loss of cilia are seen after exposure to smoke (Fig. 5B). Transmission electron microscopy of the lung septa revealed, however, normal appearance of the epithelial and endothelial surfaces and of the tight junctions of the endothelium in the smoke-exposed animals as well as the CO-exposed animals.

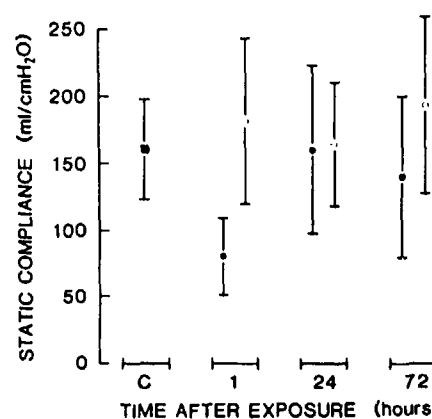


FIG. 4. Changes in static compliance were the mirror image of PR, but the observed differences were not statistically significant.

DISCUSSION

This study demonstrates that CO exposure caused no physiologic or anatomic injury to the lung, in contrast to the significant changes observed after smoke inhalation. Furthermore, the responses to smoke and CO immediately after exposure were completely different, although the CO-Hb levels of the two groups were comparable. Cardiac output in the CO group was significantly increased 1 hour after exposure (Fig. 2), an apparent compensation for the loss of available hemoglobin due to binding with CO. Lack of such a response in the smoke-exposed group may have been due to decreased venous return caused by mechanical ventilation. Elevated pulmonary resistance, a result of increased bronchial tone, decreased surfactant, and atelectasis, necessitates higher intrathoracic pressures during artificial ventilation (Fig. 3). This interpretation is supported by another series of experiments (unpublished data) in which the cardiac output immediately after smoke exposure in spontaneously breathing animals was increased by 30–60%. In the literature, however, there are conflicting reports of this response; cardiac output immediately after smoke exposure was increased in spontaneously breathing goats (15) and decreased in intubated and spontaneously breathing dogs (18). This discrepancy may be explained by differences in experimental conditions; the animals

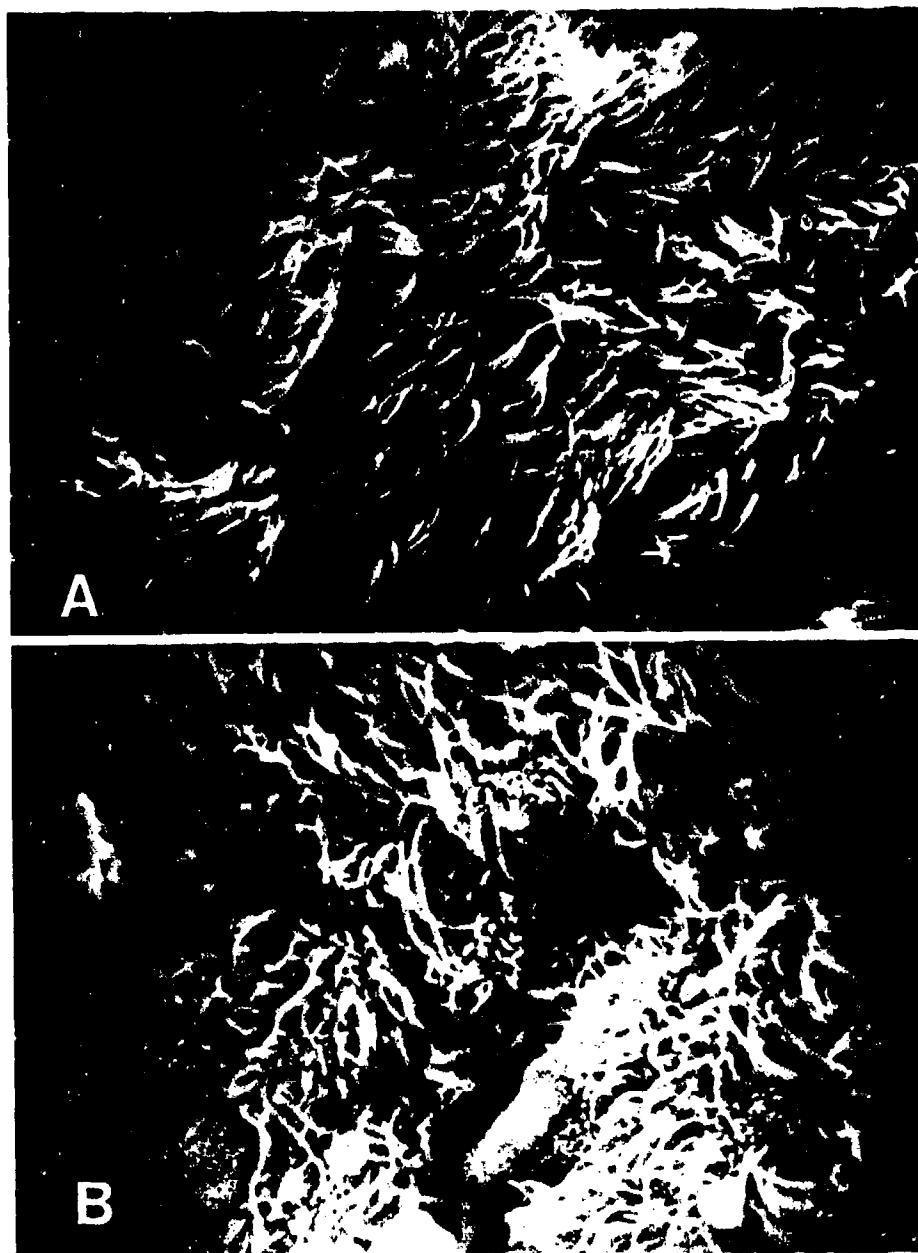


FIG. 5. Scanning electron micrograph of the tracheal surface at 24 hours after exposure ($\times 3,200$, coated with 200 A gold-palladium). Normal cilia are preserved in the CO-exposed animals (A), whereas disruption, swelling, and loss of cilia are evident after exposure to smoke (B).

were fully awake in the former study and subjected to barbiturate administration in the latter. Therefore the apparent lack of physiologic compensation in terms of cardiac output in smoke-exposed animals does not necessarily indicate suppression of cardiac function.

Smoke-exposed animals appeared to manifest an alternate means of physiologic compensation; i.e., a significant decrease in mixed-venous oxygen tension compensated for the decreased oxygen delivery and maintained oxygen consumption (Table I).

There are conflicting reports of carbon monoxide toxicity to the lung. Fein et al. demonstrated decreased lung compliance, increased airway resistance, and ultrastructural changes in epithelial and endothelial cells in rabbits exposed to 0.8% CO for 45 minutes (5). Halebian and

Robinson reported no significant changes in extravascular lung water and ventilation-perfusion distribution in dogs exposed to 1% CO for 10 minutes (7, 14). Fein's experiment, however, was associated with hypotension (mean blood pressure of 50 mm Hg) and it is quite possible that alveolar-epithelial changes were caused by shock. Other studies describing CO toxicity involved prolonged exposure to CO. Therefore, as far as acute exposure is concerned, it seems reasonable to conclude that pulmonary function and ultrastructure are not impaired by CO exposure per se (when the systemic circulation is maintained).

As Sharar et al. have pointed out, there is a great discrepancy in the peak CO-Hb levels and mortality in various animal models of isolated smoke inhalation in-

TABLE II
Large animal models of isolated smoke inhalation injury

Author (Year)	Animal	Mode of Exposure*	Smoke Material	Exposure Time	CO in Smoke (%)	Peak CO-Hb (%)	PaO ₂ (mmHg)	Mortality (%)
Stephenson (18) (1975)	dog	S	Wood	5.5-6 min	NA	NA	210 at 24 hr†	8 at 24 hr
Clark (1) (1977)	dog	F, I	Sawdust & kerosene	1 min‡	1.9	39‡	NA	NA
Walker (21) (1980)	goat	F, I	Cotton towel	6-8 min	NA	NA	NA	0 at 24 hr
Potkin (13) (1980)	rabbit	S	Wood	40 min	0.67	39.6 ± 6.1	63 ± 11	NA
Nieman (12) (1980)	dog	F, I	Sawdust & kerosene	5 min	1.7	23.3	60 at 2 hr	0 at 4 hr
Davies (3) (1983)	dog	S, I	Crude cotton	4 min	NA	58 ± 2	56 at 8 hr	NA
Herndon (8) (1984)	sheep	F, T	Cotton towel	56 breaths	NA	NA	77 ± 5 at 36 hr	8 at 72 hr
Shimazu (16) (1987)	sheep	F, I	Surgical pad	1-5 min	0.7-2.2	§	40-80	§
Sharar (15) (1988)	goat	S, (T)	Douglas fir	11-60 min	0.2-0.3	18-61	80 ± 7	0 at 24 hr

* S: spontaneous breathing, F: forced ventilation, I: endotracheal intubation, T: tracheostomy.

† Breathing 100% oxygen, PaO₂ values at the other models are under room air ventilation.

‡ Repeat exposure after 15 minutes.

§ Adjustable by changing the exposure time to smoke.

jury (15). They attribute such discrepancy to the mode of smoke exposure, i.e., spontaneous ventilation during exposure versus mechanical insufflation with smoke. Although certain animal models employing forced mechanical insufflation have a disproportionately high mortality associated with lower peak CO-Hb levels, the mode of exposure may be a relatively minor factor in the pathogenesis of smoke inhalation. First, there are animal models employing forced mechanical insufflation in which mortality is not out of proportion to peak CO-Hb levels (Table II). For example, the sheep model developed by Shimazu et al. has a peak CO-Hb level of 45% and no mortality within 72 hours. Second, Watanabe et al. have documented that higher levels of CO-Hb are required in spontaneously breathing animals to produce similar levels of pulmonary damage and mortality compared to the mechanically insufflated animals. These investigators found that spontaneously breathing animals held their breaths when exposed to heated air and that the severity of injury was influenced by hyperventilation in response to carbon monoxide (22). Third, the dose-response curve in smoke inhalation injury is not linear (16) and the relationship between mortality and CO-Hb in one model cannot be simply extrapolated to other models. Although a spontaneously breathing model is closer to the clinical situation, it suffers from variations and inconsistency among animals.

On the basis of clinical experience, the peak CO-Hb levels of the smoke inhalation models (Table II) appear to be too high. Animals recover readily from CO poisoning with peak CO-Hb levels of more than 60%, which is supposed to be a lethal level for humans (2). A major factor contributing to this difference may be the very short half-life of CO elimination observed in such animal models; the half-life of CO-Hb is approximately 50% of that of humans (15). Godin and Wagner have suggested that the CO elimination curve is biphasic consisting of an initial rapid decrease followed by a slow phase (6, 20). The first phase is recognizable only in acute exposures,

and results in the falsely short half-life value. We have demonstrated such a difference in a sheep model of CO exposure, comparing a short exposure (2% CO for 2-5 min) and a long-term exposure (500 ppm CO for 10 hours) (17). A two-compartment model accounted for the observed differences in elimination rate as related to time, suggesting distribution of CO to a poorly perfused compartment, either an extravascular space such as muscle myoglobin or an intravascular space such as the spleen. Thus, the seemingly short half-life of CO in animal models can be attributed to short exposures to smoke containing relatively high concentrations of CO. This may also explain the lesser morbidity and low mortality associated with high CO-Hb levels in the animal models of acute exposure. Tables relating CO-Hb levels to symptoms are based on clinical experience with patients exposed to low levels of CO for a long time, and do not apply to a situation of acute exposure to high concentrations of CO even when the peak CO-Hb levels are comparable.

A defined exposure of sheep to smoke produced damage to the lungs that progressed with time. Acute CO exposure resulting in equivalent CO-Hb concentrations caused no anatomic or physiologic injury to the lungs. These findings indicate that CO per se is not an essential component in the pathogenesis of smoke inhalation injury.

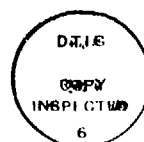
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